CHAPTER TWENTY-EIGHT 28

Chronic pancreatitis

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INTRODUCTION

Definition of chronic pancreatitis

Chronic pancreatitis is defined as a continuous or recurrent inflammatory disease of the pancreas characterized by progressive and irreversible morphological changes. It typically causes pain and permanent impairment of pancreatic function. In chronic pancreatitis areas of focal necrosis are typically associated with perilobular and intralobular fibrosis of the parenchyma, by stone formation in the pancreatic duct, and by the development of pseudocysts. Late in the course of the disease a progressive loss of endocrine and exocrine function occurs.[1,2] Several attempts have been undertaken – the last one in the year 2000 – to establish histological and morphological criteria to clearly define chronic pancreatitis. Unfortunately, an exact correlation between clinical symptoms, morphological signs, and histological criteria is still not at hand.[3,4] With an incidence of 8.2, a prevalence of 27.4 per 100 000 population, and a frequency of 0.04–5% in all autopsies performed, chronic pancreatitis represents a common disorder of the gastrointestinal tract.[5,6] Chronic pancreatitis accounts for substantial morbidity and healthcare costs. The annual treatment costs per patient are approximately US$17 000,[4] around 20 000 Americans are admitted to hospital every year with an admission diagnosis of chronic pancreatitis, and about three times as many are discharged with the diagnosis of chronic pancreatitis.[7] The 10-year survival rate of patients suffering from alcohol-induced chronic pancreatitis is 70%, while the 20-year survival rate is 45%. The mortality is thus increased 3.6-fold compared to a cohort without chronic pancreatitis.[8]

PATHOGENESIS

Pathophysiology of chronic pancreatitis

The pathogenesis of chronic pancreatitis is still poorly understood. Alcohol is the leading risk factor and the most common etiology.[9] At present there are four competing hypotheses concerning the pathogenesis of chronic pancreatitis. According to one of these hypotheses,[10] ethanol induces the fatty degeneration of acini similar to that caused by ethanol in the hepatocytes of the liver. This effect of ethanol is either a direct or an indirect toxic effect, mediated by the ethanol metabolite acetaldehyde, on the metabolism of pancreatic acinar cells.[10,11]

According to the second hypothesis,[12–14] ethanol's injurious effects involve the toxic effects of oxygen-derived free radicals on pancreatic acinar cells. Presumably, oxidative stress, caused by nicotine or ethanol, leads to the peroxidation of the lipid bilayer of the cell membrane, ultimately destroying that membrane. According to this hypothesis, an excess of free oxygen radicals would overwhelm the protective, antioxidant mechanisms as shown for some cytochrome P450 enzyme pathways in the liver. This hypothesis has stimulated several clinical studies testing antioxidants in the treatment of chronic pancreatitis and some promising observations have been reported.[12–14] A large European multicenter study testing the effect of antioxidant treatment in patients with idiopathic chronic pancreatitis is presently being launched.

A third hypothesis, proposed by Sarles and Sahel, suggests that protein precipitates in the ductal system causing ductal obstruction that leads to ductal hypertension, and that ductal hypertension ultimately causes destruction of pancreatic acini. This hypothesis asserts that chronic alcohol consumption leads to a decrease in the bicarbonate concentration and volume of pancreatic secretions and that this ultimately leads to the precipitation of protein and calcium crystals within the duct, causing duct obstruction. To avoid stone formation, it would be necessary for the acinar cells to produce a low molecular weight protein called lithostatin which would, in turn, increase the fluidity of pancreatic juice and prevent precipitation of protein plaques and calcite crystals in calcium-supersaturated pancreatic juice. The validity of this hypothesis has been questioned because others have (1) failed to find a decreased concentration of lithostatins in the pancreatic juice of patients with chronic pancreatitis or (2) could not demonstrate an inhibitory function of lithostatins on calcium carbonate precipitation. Nevertheless, the role of duct plugging in cystic fibrosis is unquestioned.[15,16]

The fourth hypothesis, originally proposed by Comfort and colleagues but then revisited by Klöppel and Maillet-Guy argues that chronic pancreatitis is a consequence of recurrent episodes of acute pancreatitis.[17] According to this hypothesis, focal fat necrosis and necrosis of the pancreatic parenchyma leads to the infiltration of lymphocytes, macrophages, and fibroblasts and fibrosis is the consequence of necrosis. This proposed hypothesis would be consistent with the concept that premature intracellular zymogen activation in pancreatic acini is the underlying cause of recurrent bouts of the acute pancreatitis that subsequently lead to the development of chronic pancreatitis. This

pathomechanism is also suspected to be the cause of hereditary pancreatitis, which is associated with mutations in the cationic trypsinogen gene.[18] Most of the clinical and experimental evidence suggests that this fourth hypothesis is the one that predicts the pathophysiology of chronic pancreatitis most accurately.

Etiology of chronic pancreatitis

In Western countries alcohol consumption is assumed to be the leading cause (70–90%) of all cases of chronic pancreatitis.[19] According to the studies from Marseilles, the logarithm of the relative risk of chronic pancreatitis increases linearly as a function of the quantity of alcohol and protein consumed. There seems to be no threshold toxicity of alcohol as identified in alcoholic liver damage. Furthermore, the type of alcoholic beverages consumed appears to be less relevant. Patients with chronic pancreatitis and alcohol-induced liver cirrhosis do not differ with regard to their daily intake of alcohol. However the duration of alcohol consumption is shorter in chronic pancreatitis. In most studies the time between the onset of alcohol abuse and first symptoms is 18±11 years. The prevalence of chronic pancreatitis clearly correlates with the alcohol consumption of a given population.[20–27]

The second most common form of chronic pancreatitis, as of today, is so-called idiopathic pancreatitis (25%).[28,29] Patients without an identifiable risk factor for chronic pancreatitis are classified as having idiopathic pancreatitis. This group has constantly decreased since Comfort and Steinberg reported in 1952 an inherited form of chronic pancreatitis following an autosomal dominant inheritance pattern.[30] Hereditary pancreatitis represents a genetic disorder closely associated with mutations in the cationic trypsinogen gene and presents with a disease penetrance of ≈80%.[31] Patients with hereditary pancreatitis develop recurrent bouts of pancreatitis which progress to chronic pancreatitis. Symptoms usually begin in early childhood but, in rare cases, the disease onset can be as late as the sixth decade of life. The severity of the acute attacks in hereditary pancreatitis ranges from mild abdominal discomfort to severe disease complicated by pancreatic necrosis, organ failure, and eventually death, although the latter course is exceedingly rare. Compared to the general population, the risk of developing pancreatic carcinoma is 50–60 times greater in patients suffering from hereditary pancreatitis.[32,33]

As hereditary pancreatitis represents an autosomal dominant disorder, it was suspected that the disease results from a single genetic defect that disrupts a critical component that protects pancreatic function in unaffected individuals. In 1996 Whitcomb et al. identified a single point mutation in the third exon of the cationic trypsinogen gene on chromosome 7 (7q35) that associates with the phenotype of hereditary pancreatitis.[31] This mutation was present in all affected individuals and obligate carriers from five kindreds with hereditary pancreatitis, but not in individuals who married into the family nor in 140 unrelated individuals. This G-to-A transition results in an arginine-(R)-(CGC)-to histidine-(H)-(CAC) substitution, referred to as R122H. It was predicted to eliminate a fail-safe trypsin hydrolysis site that is necessary to initiate the self-destruction of activated trypsin. Since 1996 several more mutations (20 so far) in the trypsinogen gene have been reported, but the R122H mutation is still the most common.[34–36] As far as the role of premature zymogen activation is concerned, the data from hereditary pancreatitis presently available are inconclusive.[37] Because trypsin activation is an event known to occur in pancreatitis,[38] and because trypsin can activate many other digestive proteases of the pancreas in vitro, previous attempts to interpret the functional consequences of trypsinogen mutations have focused on features that would either allow for premature intracellular activation of trypsinogen or permit an extended intracellular activity of trypsin. Other studies have suggested that trypsin activity may be a critical factor for the degradation of other, much more destructive digestive proteases. Trypsin activity would then have to be regarded as protective factor and hereditary pancreatitis as a disease caused by a loss, rather than a gain, of trypsin function.[34,37] The idea of digestive protease activation dates back a century to when the pathologist Hans Chiari suggested that the pancreas of patients who had died during episodes of acute necrotizing pancreatitis 'had succumbed to its own digestive properties,' and he postulated pancreatic 'autodigestion' as the underlying pathophysiological mechanism of the disease.[39] While the importance of digestive proteases in the onset of pancreatitis is now undisputed, the role of individual serine proteases in that cascade-like event, and that of the different isoforms of trypsin in particular, is still a matter of intense research and debate.[37]

Shortly after the identification of mutations in the trypsinogen gene associated with chronic pancreatitis, another important observation was made by Witt et al.[40] They found mutations in the SPINK-1 gene (encoding the pancreatic secretory trypsin inhibitor, PSTI) to be associated with idiopathic chronic pancreatitis in children. SPINK-1 mutations can frequently be detected in a cohort of patients who do not present with a family history of pancreatitis and are devoid of any classical risk factors for chronic pancreatitis.[41,42] SPINK-1 is believed to form a first line of defense in inhibiting trypsin in the pancreas. The discovery of SPINK-1 mutations therefore provides additional evidence for the role of protease activation in the development of pancreatitis.[43]

Cystic fibrosis is an autosomal recessive disorder, with an estimated incidence of 1:2500, characterized by pancreatic exocrine insufficiency and chronic pulmonary disease. The extent to which the pancreas is affected varies between a complete loss of exocrine and endocrine function to clinically normal pancreatic function. Recurrent episodes of pancreatitis occur in 1–2% of all patients with cystic fibrosis and normal exocrine pancreatic function, and more rarely in patients with exocrine pancreatic insufficiency. Compared to the population of patients without chronic pancreatitis, 16.7–25.9% of patients with idiopathic chronic pancreatitis carry mutations in the cystic fibrosis conductance regulator gene (CFTR). Thus, in addition to chronic lung disease and vas deferens aplasia, chronic pancreatitis represents a third disease entity associated with mutations in the CFTR gene. It is important to note that pancreatic exocrine insufficiency in patients with cystic fibrosis is a completely different disease entity and not to be confused with chronic pancreatitis in the presence of CFTR mutations.[44,45]

Considerable attention, especially in Japan, is nowadays paid to an only recently characterized type of steroid-responsive chronic pancreatitis termed autoimmune pancreatitis. This type of chronic pancreatitis typically presents with an enlargement of the pancreatic gland, diffuse narrowing of the pancreatic duct, elevated serum lipase levels and, in 70–80% of the patients, with

obstructive jaundice. For this reason, most patients are initially suspected to have pancreatic carcinoma. The absence of calcification of the gland is regarded as a pathognomonic feature. The gender distribution is 2:1 with a predominance in men. The incidence of autoimmune pancreatitis increases in the second decade of life. Blood tests reveal an increased IgG4 level, nuclear autoantibodies (ANA), autoantibodies directed against lactoferrin as well as against carbonic anhydrase, and elevated serum rheumatic factors. Morphologically, ductal and periductal inflammatory infiltrates, predominantly composed of lymphocytes, plasma cells, and granulocytes, are the most constant histopathological findings. In approximately 60% of cases, the disease is associated with other systemic autoimmune disorders. Endoscopic retrograde cholangiopancreatography (ERCP) examination shows a diffuse irregular narrowing of the main pancreatic duct and narrowing stenoses of the bile duct passing through the head of the pancreas. In contrast to other varieties of chronic pancreatitis, autoimmune pancreatitis responds very well to steroid treatment.[46]

Metabolic disorders associated with hypertriglyceridemia above 1000 mg/dL can be responsible for the development of recurrent episodes of pancreatitis.[47,48] In rare cases chronic calcifying pancreatitis has been reported to be due to hypercalcemia in patients with untreated hyperparathyroidism. This has become a rare cause of pancreatitis today because serum calcium levels are routinely checked and part of most automated clinical chemistry panels. The underlying mechanism of hyperparathyroidism-associated pancreatitis is most likely related to the established role of calcium in the premature, intracellular activation of digestive proteases.[49]

CLINICAL PRESENTATION

The clinical presentation of patients with chronic pancreatitis is highly dependent on the stage of the disease. It varies between severely ill patients with symptoms of acute abdomen, to slowly progressing cachexia. The cardinal symptoms, and often the first signs of the disease which prompt the patient to seek medical help, are beltlike abdominal pain that frequently radiates to the back, loss of body weight (in 80%) and steatorrhea (in less than 50%).[50] Pain is the most commonly encountered symptom in chronic pancreatitis (80–95% of all patients).[51] Some studies which investigated the natural course of the disease showed that with the duration of chronic inflammation the intensity of pain can decline. This observation was termed 'burn out of pain' and correlates frequently with the occurrence of parenchymal calcifications and the loss of endocrine and exocrine function. Pain in chronic pancreatitis can have several causes. It can be caused by inflammatory infiltrates into pancreatic tissue and its perineural sheath. Morphological studies in patients with chronic pancreatitis have demonstrated an increase in diameter and in the number of intrapancreatic nerves, foci of inflammatory cells associated with nerves and ganglia, and damage of the perineural sheath.[52] This disruption of the perineural sheath may allow inflammatory mediators to gain access to the neural elements. It is presently not known whether similar changes within pancreatic nerves also occur among patients without pain.

Several lines of clinical and experimental evidence point to increased pressure within the pancreatic duct or the parenchyma as an important cause of pancreatic pain. Both pancreatic ductal and tissue pressure are often found to be elevated in patients with chronic pancreatitis undergoing surgery for chronic pain.[53,54] Drainage of the pancreatic duct can lead to an immediate reduction in pressure to normal levels and can be associated with pain relief.[55] Although this mechanism represents an attractive hypothesis it does not explain why decreasing pancreatic secretion with somatostatin analogues results in a reduction of pain in only a minority of patients. Furthermore, there is no predictable correlation between pancreatic duct pressure and duct morphology or between pancreatic duct morphology and clinical symptoms. The mechanism by which increased intrapancreatic pressure causes pain may also involve a decrease in pancreatic blood flow, a decrease in capillary filling, and thus tissue ischemia – not unlike a surgical compartment syndrome.

Gastric or duodenal ulcers as well as meteorism due to bacterial overgrowth in the gut caused by maldigestion must also be considered as a cause of pain in patients with chronic pancreatitis.

More rarely, patients seek medical help because they developed diabetes mellitus, and the loss of endocrine function or cachexia are the initial symptoms of chronic pancreatitis. Some patients who present with symptoms and signs of acute pancreatitis due to alcohol abuse are diagnosed as suffering from chronic pancreatitis only during the hospital admission. The median age at diagnosis of patients with chronic pancreatitis is 37–40 years. Frequently, at that age patients already report a long history of alcohol abuse. At this stage patients often report episodes of pain followed by periods of relative well-being.

DIAGNOSIS

Diagnostic imaging procedures

The diagnosis of chronic pancreatitis is based on clinical data, imaging studies, and laboratory investigations including pancreatic function tests. Unlike liver or inflammatory bowel disease, nonoperative access to tissue for histologic examination is usually not possible for diagnostic purposes. Most patients are therefore subjected to clinical, imaging, and laboratory studies before the diagnosis of chronic pancreatitis is established and, since the results of these studies do not always correlate, their combination is often required (Table 28.1).

Transabdominal ultrasound can provide key information. The procedure is noninvasive and without complications but it is highly dependent on the experience of the examiner. Its diagnostic sensitivity is in the range of 52–68%, while its specificity ranges 95–100%. Most noteworthy is its negative predictive value of above 95%. Nevertheless, the value of this procedure should not be overestimated. A high specificity and sensitivity can only be achieved if the organ can be sufficiently visualized, as is the case in approximately 80% of patients.[56] In 20% of cases overlying bowel gas or adipose tissue prevents adequate visualization. The sensitivity of transabdominal ultrasound can be increased by intravenous application of the secretagogue secretin, at a dose of 100 CU. Three to 5 minutes after the infusion of secretin, the main pancreatic duct in healthy volunteers is found to dilate from a median diameter of 1.07±0.09 mm to 1.9±0.16 mm. In patients with chronic pancreatitis, the diameter of the pancreatic main duct increases only slightly or not at all after application of secretin (unstimulated 3.29±0.79 mm, stimulated 4.14±0.94mm). The reason for this absence of a dilatation is believed to be the presence of periductular fibrosis, which is found in the chronically inflamed tissue.[57]

Table 28.1 Parameters to be determined at the first visit in patients with suspected chronic pancreatitis

History and clinical examination	Blood test/ fecal test	Imaging studies
Age at onset of symptoms, first episode Frequency of episodes Duration of pain, pain diary, pain medication Steatorrhea, meteorism Weight loss Jaundice, vomiting, fever Smoking habits Etiology: Alcohol abuse Family history for pancreatitis, pancreatic cancer, cystic fibrosis affected relatives or children Hyperparathyroidism Hyperlipidemia Autoimmune disorder, e.g. RA, Sjögren's syndrome	Lipase, Amylase, CRP, Bilirubin, γ-GT, alkaline phosphatase, leukocytes, thrombocytes, red blood count, serum albumin. Blood sugar level, Insulin, C-peptide, HbA1c Triglyceride, Cholesterol Calcium, Phosphate, PTH Carbodeficient transferrin ANA, if positive, autoantibodies against lactoferrin and carboanhydrase II, IgG4. Fecal elastase In case of positive family history or onset below 25 years: genetic testing for trypsinogen mutations Ca-19-9, CEA if cancer is found	Transabdominal ultrasound: depending on the result ERCP Endoscopic ultrasound CT scan MRI/MRCP

Plain abdominal radiography is reasonably specific for the diagnosis of chronic pancreatitis when diffuse pancreatic calcifications are detected. Since calcifications occur relatively late in the natural history of chronic pancreatitis, plain abdominal radiography is inferior to transabdominal ultrasound and, even if it is inexpensive, risk free and widely available, in our opinion, it is today an obsolete procedure for the diagnosis of chronic pancreatitis.

The gold standard of noninvasive imaging in the diagnosis of chronic pancreatitis is contrast enhanced computed tomography. Computed tomography is most accurate in the detection of complications associated with chronic pancreatitis such as pancreatic pseudocysts, thrombosis of the splenic vein, a pancreatic mass, or an acute episode of chronic pancreatitis. The overall sensitivity of CT scans is 74–86%, while its specificity is 98–99%. Chronic pancreatitis is regarded as a risk factor for the development of ductal adenocarcinoma of the pancreas. The lifetime risk of a patient with alcohol-induced chronic pancreatitis for pancreatic cancer is around 4%, but the risk is greatly increased (to a cumulative risk of 40% till the age of 70 years) if the patient suffers from hereditary chronic pancreatitis (even greater if the patient smokes). Contrast enhanced CT appears to be the most accurate and reliable imaging procedure for the detection of early stage, resectable, pancreatic carcinoma (Fig. 28.1).[58,59]

Endoscopic retrograde cholangiopancreatography (ERCP) is generally considered to be the most specific and sensitive test of pancreatic duct morphology. ERCP has become the gold standard for the diagnosis of chronic pancreatitis. The overall sensitivity of ERP is 93–99%, while the specificity is 85–100%. In addition to its accuracy in detecting changes in the main pancreatic duct and its side branches, ERCP can be used to assess the macroscopic appearance of the papilla of Vater and to take biopsies for histological examination. ERCP is not only a diagnostic tool; it also offers the possibility of treatment. Pancreatic pseudocysts, for example, can be drained through the pancreatic duct by insertion of an endoprosthesis and obstructing stones can be endoscopically removed. To uniformly evaluate and accurately diagnose chronic pancreatitis, the so-called Cambridge classification of duct changes on ERCP for patients with chronic pancreatitis was agreed upon in 1984 (Table 28.2). It must be kept in mind that ERCP is an invasive procedure with a complication rate of up to 5% (10% in certain subgroups) and that the procedure is associated with a mortality of 0.1–0.5%.[60–64]

Endoscopic ultrasound has recently emerged as an important tool in the diagnosis of pancreatic disease. Frequently, ERCP-detected changes in the parenchyma of the pancreas precede changes in the pancreatic duct. Endosonography is a sensitive and valuable procedure for the detection of early changes in tissue morphology and it avoids some of the disadvantages of transabdominal ultrasound, i.e., intervening gas in the gut.[62,65,66]

The sensitivity of magnetic resonance cholangiopancreatography (MRCP) varies between 70% and 92% if ERCP is used as the gold standard. The fact that MRCP has a lower complication rate than ERCP and is less investigator dependent than ultrasound will, in the future, lead to its increased use as a diagnostic procedure for chronic pancreatitis in spite of its cost and its inherent lack of therapeutic options (Table 28.3).[60]

Pancreatic function tests

Tests for exocrine and endocrine pancreatic function serve as a second line of diagnostic tools for chronic pancreatitis. Exocrine insufficiency is defined as either global or partial diminution in the pancreatic secretion of amylase, lipase, proteases, and bicarbonate. The most common etiology for this loss of exocrine function in adults is chronic pancreatitis. The human pancreas has a substantial exocrine reserve. Clinical symptoms of exocrine insufficiency do not occur until pancreatic lipase secretion is reduced to less than 10% of normal.[67] A clinically relevant

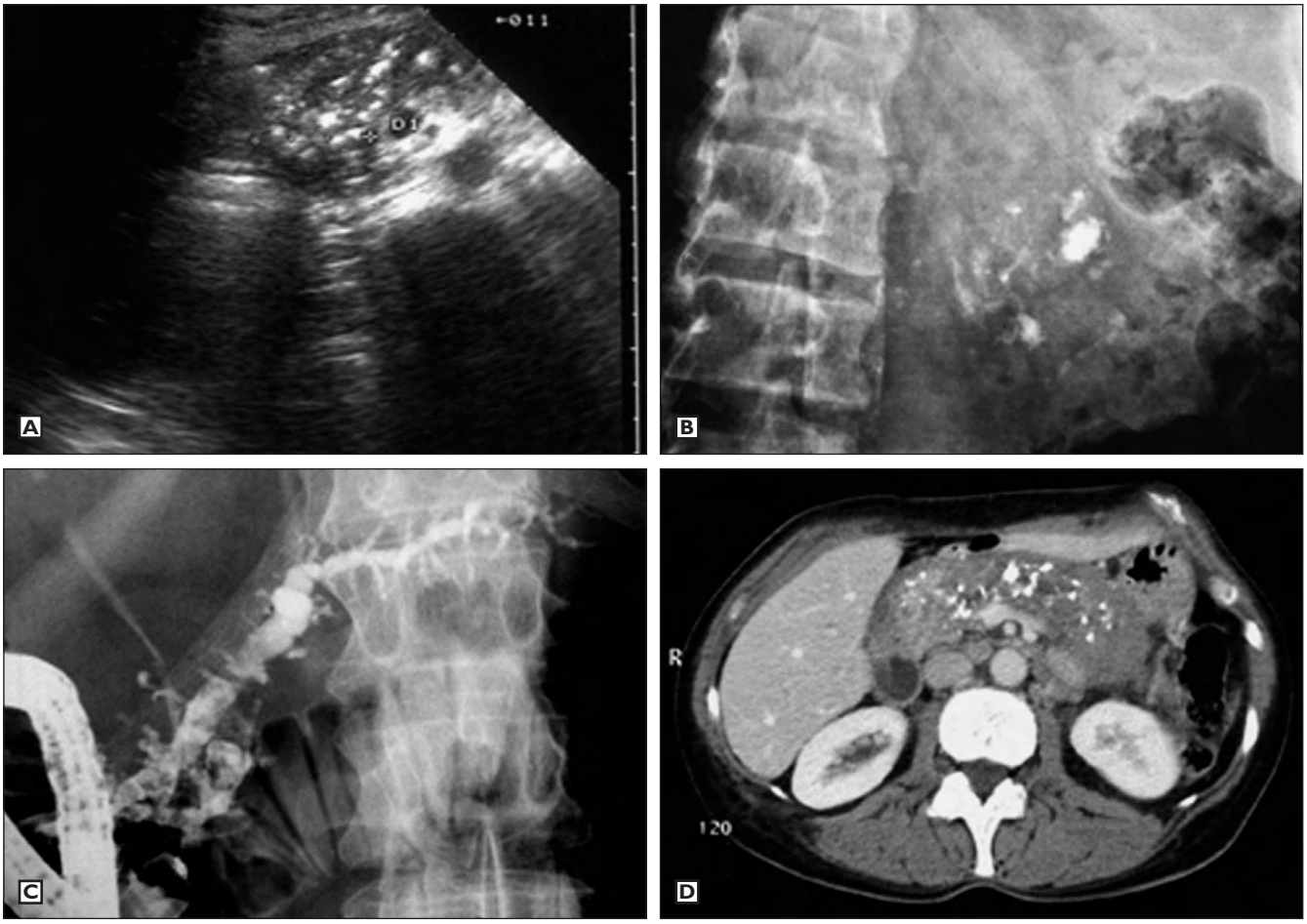

Fig. 28.1 • Typical morphological signs of advanced calcifying chronic pancreatitis. **(A)** Transabdominal ultrasound with numerous calcifications in the pancreatic head. **(B)** Plain abdominal radiography with multiple calcifications. **(C)** Endoscopic retrograde cholangiopancreatography (ERCP) with dilated pancreatic duct and filling defects as well as more than three altered side branches displaying irregularities. In the head of the pancreas a filling defect in the main pancreatic duct can be observed most likely resembling a pancreatic duct stone. **(D)** Contrast enhanced computer-tomography with an enlarged pancreatic gland, dilated pancreatic main duct and numerous calcified spots.

Table 28.2 Classification of chronic pancreatitis according to morphological criteria

	Cambridge classification of ERCP	Ultrasound/CT scan
Normal	No signs of pathological changes	
Grade I, mild	> 3 pathological side branches of the main pancreatic duct	Two of the following pathological findings: Cysts Duct irregularities Focal acute pancreatitis Heterogeneity of the parenchyma Increased echogenity of the ductal wall Intraductal filling defects Gland enlargement
Grade II, moderate	> 3 pathological side branches of the pancreatic duct + dilated main pancreatic duct	All above-mentioned findings
Grade III, severe	Grade II plus one or more of the following findings: Cyst >10 mm Intraductal filling defects Calcification Obstruction or strictures of the pancreatic duct Dilatation of the pancreatic duct as well as irregularities Contiguous neighboring organ invasion	

Table 28.3 Sensitivity and specificity of routinely employed techniques for the diagnosis of chronic pancreatitis (after ref. 55)

Diagnostic tool	Sensitivity	Specificity
Transabdominal ultrasound	48–90%	75–90%
Contrast enhanced CT scan	56–95%	85–90%
ERCP	68–93%	89–97%
Endosonography	88–100%	90–100%
Fecal elastase-1	50–93%	62–93%
Serum pancreolauryl test	70–82%	70–87%
Secretin-cholecystokinin test	80–90%	90–95%

The wide range of percentages given for specificity and sensitivity of diagnostic procedures results from a heterogeneous cohort of patients as well as the different mix of severity of cases in the studies used. Furthermore, a gold standard has so far not been defined.

Table 28.4 Direct and indirect pancreatic function tests

	Pancreatic function test
Direct	Secretin-cholecystokinin test Endoscopic secretin test
Indirect	Serum tests: Pancreolauryl test NBT-PABA test (discontinued) Fecal tests: Fecal elastase-1 Chymotrypsin Stool weight Fecal fat quantification

maldigestion can be found in about one-third of all patients with chronic pancreatitis. Reduced exocrine function often precedes morphological changes and, therefore, sensitivity for the detection of early changes is higher for pancreatic function tests than for imaging studies.

Several tests of exocrine pancreatic function are well established in the diagnostic evaluation of patients suspected to have chronic pancreatitis. The approaches can be divided into those that are direct and those that are indirect. When pancreatic function is measured directly, the stimulated secretion of pancreatic juice is collected via a nasoduodenal tube and then the enzymes and bicarbonate are quantitated. Indirect methods detect decreased secretion by measuring the amount of pancreatic enzymes in stool or serum or, alternatively, they evaluate the digestion of synthetic substrates by pancreatic enzymes (Table 28.4). The disadvantage of indirect tests for pancreatic function is that they cannot distinguish between structural or functional abnormalities. The situation after gastrectomy can serve as a good example. In this case, an impaired synchrony of pancreatic secretion and the gastrointestinal passage of food may lead to clinical exocrine insufficiency or abnormal function tests without primary damage of the pancreas (pancreatico-cibale asynchrony).[68]

Direct pancreatic function tests

Secretin-cholecystokinin-test: Pancreatic enzyme activity as well as bicarbonate concentration are measured in the duodenal juice after stimulation with the enterohormones secretin (1 CU/kg, i.v.) and cholecystokinin (CCK 25–100 ng/kg). This requires passing a nasoduodenal tube that has two lumena. The proximal one is used to remove gastric secretions and to prevent gastric juice from stimulating pancreatic secretion. The second lumen is placed beyond the ligament of Treitz and fractions, containing duodenal juice, are aspirated every 15 min. The secretin-cholecystokinin test is the gold standard for pancreatic function testing. Its overall sensitivity and specificity is 90%. Even though the secretin-cholecystokinin test is the most accurate assay for pancreatic function, only few specialized centers routinely use this technique for clinical studies. The cost of testing one patient is about US$150. Furthermore, 2 days of labor by the technician are required to prepare the test and to do the analysis.[69–71] Some authors use a standardized test meal (Lund test) rather than hormone stimulation of the exocrine pancreas but this more 'physiological' approach is, ultimately, less sensitive in detecting early functional changes and bicarbonate cannot be measured in the collected chyme.

Indirect pancreatic function tests

Fecal elastase-1: Pancreatic elastase accounts for 6% of all proteins in pancreatic juice. Compared to other serine proteases, this enzyme is highly stable during its passage through the gut and can be detected in stool (median concentration of 1200 μg/g). Fecal elastase is measured using an enzyme linked immunoassay (ELISA) and there are polyclonal and monoclonal test kits commercially available. The ELISAs employed have been extensively evaluated for cross-reactivity between species and none has been found. It is therefore not necessary for the patient to discontinue enzyme supplementation treatment with animal-derived enzyme preparations. To measure fecal elastase, only small amounts of stool are required (100 mg) and it is not necessary to test multiple samples because interassay variability is low (8–15%). The overall sensitivity of fecal elastase testing is 63% for mild exocrine insufficiency and it rises to 100% for intermediate and severe exocrine insufficiency if compared to the gold standard of the secretin-cholecystokinin test.[72,73]

Pancreolauryl: The serum pancreolauryl test (PLT) is the most widely accepted oral indirect pancreatic function test for detecting and grading the functional impairment of the gland. The test involves ingestion of fluorescein dilaureate (0.25 mmol) with a standardized breakfast (20 g bread, 20 g butter, and 200 ml tea). The fluorescein dilaureate is cleaved in the duodenum by pancreatic esterases and fluorescein, absorbed from the intestine, can be photometrically measured in the patient's urine or serum after defined time intervals. Before performing this pancreatic function test, the patient must discontinue enzyme supplementation as orally taken enzymes interfere with testing, leading to false-negative results. The pancreolauryl test can also quantify severe exocrine insufficiency via a diminished increase in serum fluorescein or in dialysis fluid of patients with renal insufficiency.[74] The sensitivity is 82% with a specificity of 91% for severe exocrine insufficiency. Mild exocrine insufficiency can only be detected with a sensitivity of 51%. The PLT is regarded as an indirect noninvasive pancreatic function test of high clinical relevance.[75]

Fecal fat: Fecal fat quantification by the classical Van de Kamer (alcohol extraction) technique is the standard for establishing the presence of steatorrhea, i.e., characteristic symptom of reduced exocrine function. The test is performed by collecting stool over 3 days during which oral fat intake is 80–100 g/d. After a 90% loss of exocrine function, fat excretion in stool significantly increases as a sign of fat maldigestion. A mild or intermediate impairment of exocrine function is usually clinically compensated.

Pancreatic endocrine function should be evaluated by fasting and 1 h postprandial blood glucose levels and oral glucose tolerance testing as well as HbA1C according to the guidelines of the WHO for the diagnosis of diabetes mellitus.

In addition to an evaluation of exocrine and endocrine function, considerable attention should be paid to the etiology of the disease. Recent results from molecular and genetic studies suggest that a significant number of patients with chronic pancreatitis suffer from a genetically determined or inherited disease. This is mainly true for patients who were formerly classified as suffering from idiopathic pancreatitis, for patients with an onset of the disease before the age of 25, or for those with a positive family history for chronic pancreatitis or pancreatic cancer. Patients who suffer from chronic pancreatitis due to mutations in the cationic trypsinogen gene are burdened with a 70- to 140-fold increased risk of developing pancreatic cancer, particularly if they smoke. Whether this is also true for patients who carry SPINK-1 or CFTR mutations needs to be determined. Genetic testing for trypsinogen gene mutations can be recommended for chronic pancreatitis patients who have first-degree relatives suffering from pancreatitis or pancreatic cancer, and for patients with chronic pancreatitis or recurrent bouts of acute pancreatitis before the age of 25 years and no identifiable risk factor.[76] Genetic testing for clinically unaffected relatives is not indicated and should only be performed within ethics committee-approved research protocols.

TREATMENT STRATEGIES

The aim of medical treatment of chronic pancreatitis is the compensation of exocrine and endocrine pancreatic insufficiency. It is, therefore, dominated by attempts to control maldigestion, steatorrhea, weight loss, and blood glucose levels and to achieve adequate pain management. The role and prognostic value of psychosocial care with the aim of discontinuing alcohol abuse in patients with chronic pancreatitis should not be underestimated.

Pain management

Following intrapancreatic protease activation or tissue necrosis, inflammatory mediators are locally released. These not only facilitate and sustain the inflammatory process, but they can also exert a direct effect on sensory fibers of the celiac plexus (T5–T9), thus triggering visceral pain, which is a common symptom in patients with chronic pancreatitis. Adequate pain relief is therefore one of the most important and urgent treatment goals. There are several concepts to pain treatment which need to be carefully evaluated on an individual basis. In principle, pain management for chronic pancreatitis follows the guidelines of the WHO for the treatment of chronic pain. The combination of a nonsteroidal analgesic with a centrally active drug should initially be considered. Concerns that morphine analogues may negatively affect the course of chronic pancreatitis because of their effect on the sphincter of Oddi are unwarranted. Some authors prefer meperidine over other opiates in pancreatitis but this alleged advantage has not been studied in controlled trials. Tramadolsulphate, as an alternative to other opiates, should not be considered in patients with acute or chronic pancreatitis because, according to the authors' personal experience, nausea and vomiting are common side effects in this group of patients. As many patients with chronic pancreatitis are drug addicts, a rigid scheme of pain medication is more effective than medication on demand. Several studies have suggested that enzyme supplementation is associated with pain relief. A randomized, placebo controlled study, however, has not shown such a beneficial effect (Table 28.5).[77,78]

Diabetes mellitus associated with chronic pancreatitis

Diabetes mellitus is an independent predictor of mortality in patients with chronic pancreatitis. Morbidity and mortality due to diabetes mellitus may occur from progressive microangiopathic complications or from more acute complications such as treatment-induced hypoglycemia, particularly in those patients with an inadequate glucagon reserve. Ketoacidosis is relatively unusual. This may be due to the fact that insulin secretion has not entirely ceased when glucagon secretion is already reduced. The underlying pathophysiology of diabetes in chronic pancreatitis is the loss of insulin secretion. Oral antidiabetic agents, therefore, have no role in the treatment of diabetes due to chronic pancreatitis. Control of blood sugar levels should be achieved with exogenous insulin. Guidelines for the treatment and monitoring of the secondary organ failure of type I diabetes mellitus can be used for the treatment of pancreatitis-induced diabetes, but the insulin doses required are usually lower.[79,80]

Nutrition and pancreatic enzyme supplementation

Enzyme supplementation is clinically indicated if patients suffering from chronic pancreatitis lose more than 10% of their body weight, excrete more than 15 g/d fat with their stool, or suffer from clinical symptoms of dyspepsia or meteorism. Treatment of the pain and meteorism associated with chronic pancreatitis and meteorism are two situations in which pancreatic enzymes can be used on an individual basis but there is no conclusive evidence of benefit from controlled trials. Four types of pancreatic enzyme preparation are currently available. Most commercial preparation consists of pancreatin, which is the shock-frozen powdered extract of porcine pancreas containing lipase, amylase, trypsin, and chymotrypsin. Enzyme supplements are not absorbed from the gastrointestinal tract. Rather, they are inactivated by enteral bacterial flora or digestive secretion and fecally eliminated. Administration of acid-stable, encapsulated microspheres or microtablets filled with pancreatic enzymes has greatly increased the efficacy of enzyme supplementation in chronic pancreatitis. Patients with documented exocrine insufficiency should eat three main meals a day and three snacks in between. In general, 25 000 to 50 000 IU of lipase should be ingested simultaneously along with a main meal and 25 000 IU of lipase along with the snacks. They should not be taken either

Table 28.5 Dosage of pain medication in chronic pancreatitis according to the AGA guidelines[77]

Generic	Dosage	Maximal dosage/day
Paracetamol	2–3 × 500–1000 mg	4000 mg
Metamizol	1–4 × 500–1000 mg	4000 mg
Tramadol	4 × 100 mg, 2–3 200 mg (ret)	400 mg (600 mg ret)
Buprenorphin	3–4 × 0.2–0.4 mg	6–9 μg/kg bodyweight
Pentazocin	6–7 ×50 mg	360 mg
Tilidin	3 ×50–200 mg	600 mg
Morphine	Dependent on the effect on pain relief	No maximal dosage given
Levopromazin	3–5 × 10 mg	300 mg
Clomipramin	1 × 50–100 mg	100 mg

before or after the meals. When gastric hyperacidity is present, proton pump inhibitors or H_2 antagonists should be prescribed to delay enzyme inactivation. In cases of progressive maldigestion and steatorrhea, it can be necessary to supplement lipid-soluble vitamins parenterally. In cases of severe exocrine insufficiency, one-third of the daily caloric intake can be met by administration of medium-chain triglycerides, which do not require lipolysis by lipase for absorption. While this is clinically effective, MCT fat is usually disliked by the patients because of its poor taste. The efficacy of enzyme supplementation is demonstrated by the improvement of symptoms and not by laboratory tests.[67,81–85]

Endoscopic therapy

Common bile duct stenting: Many studies which have investigated the natural course of chronic pancreatitis have shown that 30–60% of all patients undergo surgical intervention at some point in the disease process. However, this varies greatly among countries depending whether chronic pancreatitis patients are initially seen by surgeons (e.g., UK, high rate of operations) or physicians (e.g., Switzerland, low rate of operations). Approximately two-thirds of all patients can be managed conservatively or with endoscopic intervention. In 10–40% of patients, a stenosis of the common bile duct occurs that requires either endoscopic or surgical intervention. Either endoscopic or surgical intervention is clinically indicated if the patient presents with jaundice or recurrent bouts of cholangitis, to prevent secondary biliary cirrhosis. It may also allow the clinician to determine whether the common bile duct stenosis in chronic pancreatitis is the cause of pain. Several studies have examined the cost-effectiveness and the outcome of stenting of the common bile duct. They have concluded that endotherapy is initially equivalent to surgery for short-term symptom control and immediate decongestion but that only one-third of patients benefit in the long term. On the other hand, endotherapy is less invasive and is probably associated with less severe complications than surgery. It can thus be offered to patients as initial treatment with an immediate effect and an approximately 30% chance of a long-term benefit. It may be required as an emergency procedure for patients with cholangitis or as the definitive treatment for patients unfit for surgery. However, it needs to be kept in mind that long-term insertion of biliary stent can also increase the risk of cholangitis and biliary sepsis. For several decades clinicians used antibiotics or ursodeoxycholic acid to prevent clogging of the endoprostheses. Even antibiotic-coated stents were used for this purpose. It has recently been shown that this treatment does not reliably extend the patency of plastic stents. The only way to effectively prevent stent clogging is to insert a large-bore endoprosthesis and to replace the stent at least every three months. The insertion of self-expanding metal wire stents is clinically not indicated for the treatment of benign bile duct strictures in patients with chronic pancreatitis (Table 28.6).[63,86–90]

Stenting of the main pancreatic duct: Whether endoscopic decompression of Wirsung's duct is clinically indicated in the treatment of chronic pancreatitis patients with a dominant stenosis is still a matter of debate. No single prospective randomized controlled trial has shown a beneficial therapeutic effect on the metabolic complications of chronic pancreatitis after ductal decompression by endoprosthesis. The primary outcome of pain relief was addressed in a study by Dite and coworkers. They showed, in a prospective, randomized trial comparing endoscopic and surgical therapy for pain management in chronic pancreatitis, that surgery is superior to endotherapy for long-term pain relief but immediate pain relief can be achieved by endoscopic decompression.[88] A beneficial effect of endoscopic stenting was confirmed by a large retrospective multicenter study enrolling 1000 patients on an intention to treat basis.[90] Pain relief was achieved in this cohort in 65% after endoscopic decompression of the pancreatic duct and patients remained pain-free over the

Table 28.6 Indications for endoscopic biliary stenting

For symptomatic relief of cholestasis and jaundice
To drain infected bile and treat or prevent cholangitis
To gain time for repression of a reversible inflammatory process or pseudocyst
To prevent secondary biliary cirrhosis
To differentiate between pancreatic pain and pain caused by biliary obstruction

observation period of at least 2 years. However, there is evidence that stenting of the pancreatic main duct can damage the ductal epithelium, causing a continuous inflammatory stimulus that subsequently progresses to fibrosis and stricturing of the duct.[88] Due to its low degree of invasiveness and its immediate success in pain management, endotherapy can be offered as a first-line treatment. Surgery could then follow after stent failure or in cases of recurrence.

For patients with intraductal pancreatic stones, a naso-pancreatic drain should be inserted before extracorporeal shock wave lithotripsy of the stones and endoscopic removal of the fragments.[55,91–94] Pancreatic pseudocysts which impress the stomach wall can be drained by endoscopic ultrasound-guided, pigtail drainage into the stomach.

Extracorporal shock wave lithotripsy for pancreatic duct stones: Before the introduction of extracoporal shock wave lithotripsy (ESWL) in 1989, open surgery was the only option for treating pancreatic duct stones which were not accessible to endoscopic removal. Several retrospective studies have since investigated the clincal benefit of ESWL for the treatment of pancreatic duct stones. These studies were not able to demonstrate an advantage for ESWL when compared to surgical intervention. We therefore conclude that ESWL is technically feasible, it is associated with a low complication rate, a low morbidity, and nearly no mortality and it results in an immediate benefit for the patient if technically successful. The results of long-term studies, however, favor surgical intervention.[88,95,96]

Endoscopic treatment of pancreatic pseudocysts: Approximately 25% of patients with chronic pancreatitis develop pancreatic pseudocysts, mainly after an acute episode of the disease. This number is derived from a Swiss longitudinal study investigating the incidence of pseudocysts in a cohort of 245 patients with alcoholic chronic pancreatitis.[1] In the first 6 weeks 40% of pancreatic pseudocysts resolve spontaneously, while in 20% of cases complications such as bacterial superinfection, compression of neighboring organs, hemorrhage, persistent inflammation of the pancreas, or rupture of the pancreatic pseudocyst can occur. If a pseudocyst persists for more than 12 weeks, spontaneous regression is unlikely and the complication rate rises to 60%. Several recent studies have documented that the rate of complications rises when the diameter of the pseudocysts exceeds 5 cm. Smaller cysts and asymptomatic cysts can be safely monitored for at least 12 weeks. When pseudocysts become symptomatic or when they persist for more than 3 months, either surgical or endoscopic decompression should be considered. Endoscopic and surgical drainage procedures have both been shown to be effective in terms of technical feasibility and recurrence rate. In general, endoscopic intervention is used as a first-line treatment because it is less invasive and has a lower morbidity. Endoscopic drainage can be performed via the gastric or intestinal wall or through the pancreatic duct. The lowest complication rate is achieved if the pseudocyst can be drained into the stomach via a pigtail catheter. Although percutaneous pseudocyst drainage was first performed in 1867 and can be safely performed using ultrasound- or CT-guided techniques, it has been more or less abandoned because of the higher risk of secondary infection, the risk of persistent pancreatic fistulas, and the high recurrence rate. The percutaneous complication rate is twice that of internal endoscopic or surgical drainage.[97–99]

Surgical management

Surgical treatment for chronic pancreatitis is clinically indicated if intractable upper abdominal pain is refractory to conservative pain management or when organ complications occur. If pain is the leading symptom and imaging studies exclude other secondary complications of chronic pancreatitis, bilateral thoracoscopic splanchnicectomy can be performed for pain control. In 1943 Mallet-Guy described pancreatic denervation in the treatment of chronic pancreatitis pain. In 1993 the technique was rediscovered and modified as a video-endoscopic-assisted, minimally invasive treatment procedure. In a prospective randomized single-center study, it has been shown that bilateral thoracoscopic splanchnicectomy can lead to effective long-term pain relief with only 7% morbidity in patients who achieve temporary pain relief from peridural analgesia.[100–102]

In addition to refractory pain, the indications for surgery in chronic pancreatitis are closely related to complications that result from an enlarged, inflamed pancreatic head. These include obstruction of the common bile duct, stenosis of the pancreatic duct, obstruction of the duodenal loop and, in rare cases, compression of the portal vein. It should also be noted that in a retrospective analysis the incidence of pancreatic malignancy was 6–14% in a cohort of more than 200 patients with chronic pancreatitis who were originally operated on for an inflammatory mass in the head of the pancreas.[103]

One recent study has shown that early surgical intervention can delay the loss of exocrine and endocrine function in patients with chronic pancreatitis.[104] Surgical procedures include drainage operations, organ preserving procedures, and major pancreatic resections. The classical Kausch-Whipple procedure was long regarded as the standard procedure for chronic calcifying pancreatitis. During the last two decades it has been steadily replaced by more procedures which are more organ-preserving, such as the pylorus-preserving Whipple procedure according to Longmire-Traverso (pp-Whipple), the duodenum preserving pancreatic head resection (DPPHR) according to Beger and, when extended by a longitudinal pancreaticojejunostomy by the so-called Frey procedure.[105]

When deciding upon a suitable surgical procedure, one must distinguish between two different disease manifestations of chronic pancreatitis: large duct disease in which the duct of Wirsung is dilated to more than 7 mm; and small duct disease without a dilated pancreatic duct. In large duct disease, drainage procedures such as the longitudinal pancreaticojejunostomy according to Partington-Rochelle or a Puestow procedure can be performed. Both procedures are employed when pain generation is considered to be the result of increased intrapancreatic ductal and parenchymal pressure. Both include a Roux-en-Y jejunal loop to decompress the pancreatic main duct and the duct of Santorini along with the parenchyma. The procedures are associated with low perioperative morbidity and mortality, but long-term pain relief can be achieved in only 60% of cases.[106]

Because the inflamed pancreatic head is regarded as the pacemaker for the generation of pancreatic pain, and because most pancreatic islets are found in the pancreatic tail, a pancreatic left resection is rarely considered as an option. It is clinically indicated only for persistent or complicated pancreatic pseudocysts or for chronic pancreatitis confined to the tail of the gland.

Classical resective procedures can also be successfully performed in patients with small duct disease. For many years, a pancreaticoduodenectomy (Kausch-Whipple procedure), was regarded as the standard surgical procedure for chronic pancreatitis with complications arising from the pancreatic head, even if the results were burdened with a high perioperative morbidity and mortality rate of up to 44%. More recent studies have shown that hospital mortality has fallen to below 5% and that it may be less than 1% in large specialized centers. Although the classical Kausch-Whipple resection is successful in achieving pain relief in chronic pancreatitis, it is unfortunately associated with a high postoperative morbidity and a poorer long-term surgical result. The Kausch-Whipple procedure is associated with a number of side effects which may alter quality of life. Dysbalanced intestinal motility, including dumping, frequently results from the procedure. Peptic ulcers can arise at the site of the anastomosis as a result of gastrin secretion in the remaining stomach, and reflux of bile occurs due to the removal of the pylorus. Many patients complain about dyspeptic symptoms. In approximately 20% of patients, endocrine function gradually declines after the Kausch-Whipple operation, and the resulting diabetes mellitus is responsible for much of the late postoperative morbidity and mortality. To address the drawbacks of the classical Kausch-Whipple operation, during the last two decades organ-preserving techniques such as the pylorus-preserving Whipple have evolved as an attempt to minimize the disadvantages of the classical procedure. Dumping as well as peptic ulcers and reflux of bile is reduced by the pp-Whipple procedure, and the continuity of the gastrointestinal tract is less affected. Up to 90% of all patients gain weight after the pp-Whipple but up to 50% of patients still suffer from delayed gastric emptying associated with a delayed weight gain and a slightly increased risk of developing cholangitis. However, 45% of patients still lose their remaining exocrine and endocrine function regardless of the operation. Originally, the pp-Whipple procedure was created to treat pancreatic malignancies with adequate oncological radicality. In general, an extended resection, as in the Whipple procedure, is clinically not indicated for a benign disorder such as chronic pancreatitis. In 1972 H.G. Beger established the so-called duodenum preserving pancreatic head resection as a new surgical approach to chronic pancreatitis. With this procedure the anatomical structures of the gastrointestinal tract are not altered and their continuity is not disturbed. In a high-volume single center, duodenum preserving pancreatic head resection was noted to result in pain relief over 5 years in 80% of cases and the perioperative mortality was 0.7%. More than 70% of patients were resocialized into daily work routine and, only in rare cases, the loss of endocrine function progressed.[103] In 1985 Frey and Smith extended the duodenum preserving pancreatic head resection by adding a longitudinal pancreaticojejunostomy and, in this manner, combined the organ preserving surgical procedure with a drainage operation.[107] In a randomized prospective single-center study with a median observation period of 2.5 years, the Beger procedure and the Frey procedure were shown to result in equivalent postoperative outcome.[108]

In 1998 Izbicki suggested a modification of the Frey procedure for the treatment of chronic pancreatitis without a dilatated pancreatic duct.[109] He performed a V-shaped resection of the ventral pancreas to drain the second- and third-order pancreatic ducts via a longitudinal pancreaticojejunostomy. In a small group of patients and with an observation period of 30 months he was able to show that his modification resulted in complete pain relief in 95% of cases. In 67%, the quality of life increased and the procedure was associated with a low perioperative morbidity rate of 15.4% and no mortality rate.[109] Recently, Büchler et al. modified the Beger procedure to allow the resection of the pancreatic head without transection of the gland over the superior mesenteric vein. In this manner the risk of bleeding complications (especially in patients with portal hypertension) is thought to be minimized while still allowing an excision of the pancreatic head.[110] Future randomized prospective trials will have to evaluate the more recently modified techniques.

It is still a matter of debate whether a prophylactic perioperative application of somatostatin analogues can reduce the rate of leakage from the pancreaticojejunostomy. Leakage at that anastomosis results in an increased mortality and frequently requires interventional treatment. The incidence of leakage at the site of the pancreaticojejunostomy is reported to be 0–30%. In 2001, Li-Ling and Irving demonstrated, in a meta-analysis of all randomized trials, a significant reduction of pancreatic fistulas when a somatostatin analogue was perioperatively administered. The rate of reduction in leakage at the site of anastomosis was as high as 40%.[111] The route of application and the duration required are still being discussed but three doses of 100 μg of sandostatin a day for at least 5–7 days is often regarded as the standard protocol.[112]

In summary, the most widely accepted organ-preserving technique is now the duodenum preserving pancreatic head resection and this procedure should be preferred for the surgical treatment of chronic pancreatitis with complications arising from the pancreatic head.[87,103,104,110]

SUMMARY

With an incidence of 8.2 and a prevalence of 27.4 per 100 000 population, chronic pancreatitis represents a frequent disorder of the gastrointestinal tract. In the past, chronic pancreatitis was considered to be mostly associated with chronic alcohol abuse. During the past two decades idiopathic chronic pancreatitis and, moreover, hereditary pancreatitis have been recognized as distinct disease entities. Hereditary pancreatitis is an autosomal dominant disorder with an 80% penetrance. It is associated with recurrent episodes of pancreatitis starting in early childhood and associated with an increased risk of pancreatic cancer. The pathophysiology of chronic and hereditary pancreatitis is not fully understood. Patients suffering from chronic pancreatitis present with beltlike abdominal pain, weight loss, steatorrhea, and, often, diabetes mellitus. Usually the diagnosis is made by a combination of imaging procedures such as ultrasound and endoscopic retrograde cholangiopancreatography, and exocrine and endocrine function tests. Therapy is presently restricted to symptom control for the lack of a causal treatment strategy. Thirty to 60% of all patients develop disease-associated complications such as persistent pain, strictures of the common bile duct, or pancreatic duct stones that may require either endoscopic or surgical treatment.

Figures 28.2 and 28.3 provide algorithms for the diagnosis of chronic pancreatitis and treatment of chronic pancreatitis, respectively.

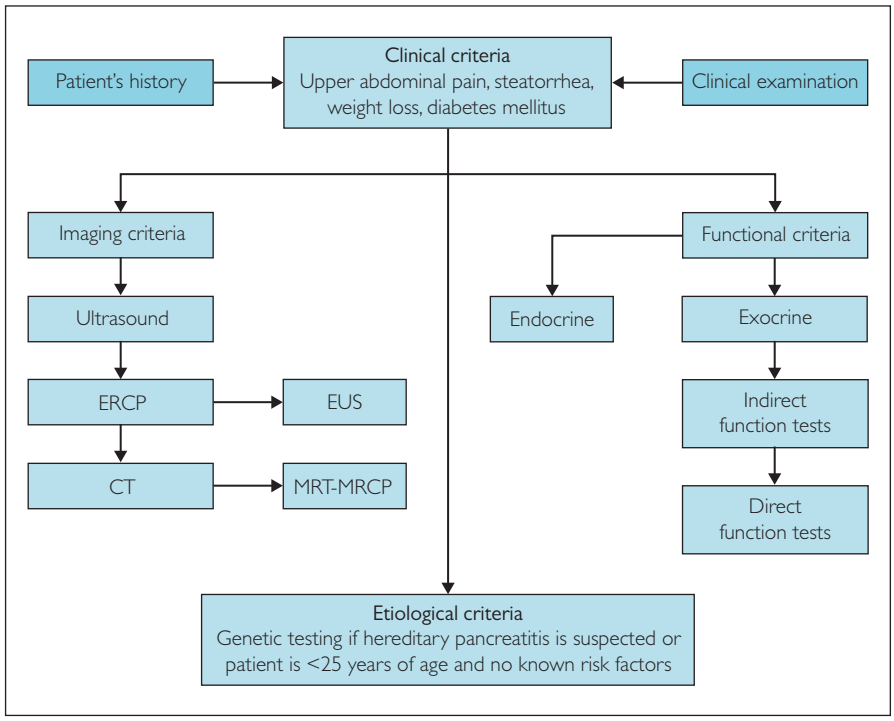

Fig. 28.2 • The diagnosis of chronic pancreatitis.

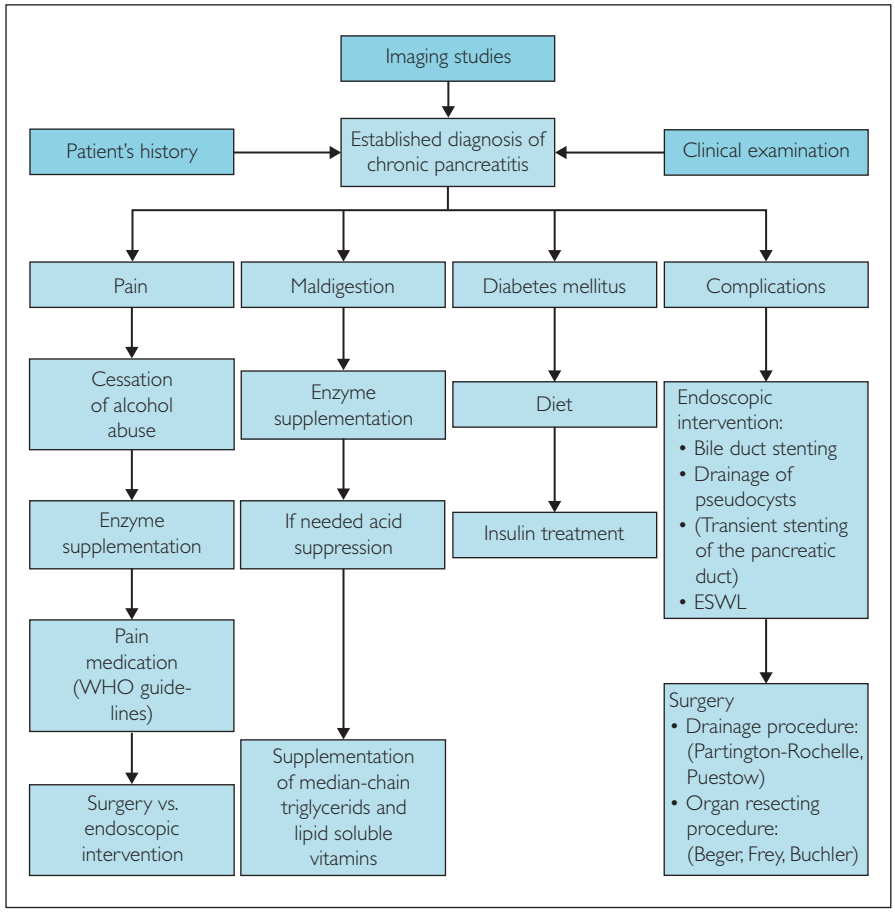

Fig. 28.3 • The treatment of chronic pancreatitis.

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